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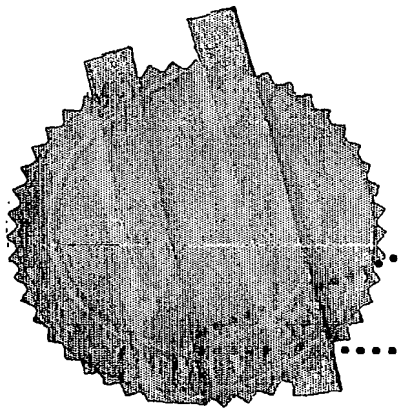
Government Of India
Patent Office
Todi Estates, 3rd Floor,
Lower Parel (West)
Mumbai – 400 013

THE PATENTS ACT, 1970

IT IS HEREBY CERTIFIED THAT, the annex is a true copy of Application and Provisional Specification filed on 20/11/2003 in respect of Patent Application No.1199/MUM/2003 of Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India, An Indian Company registered under the Companies Act 1956.

This certificate is issued under the powers vested in me under Section 147(1) of the Patents Act, 1970.



Dated this 18th day of January 2005.

(R.BHATTACHARYA)
ASSTT.CONTROLLER OF PATENTS & DESIGNS

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)

APPLICATION FOR GRANT OF A PATENT

[See sections 5(2), 7, 54 and 135 and rule 33A]

1. We, Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India an Indian Company registered under the Companies Act 1956

2. hereby declare:-

a) that we are in possession of an invention titled 'A Process for Novel Polymorphs of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride and mesylate salts'
b) that the Provisional Specification relating to this invention is filed with this application.
c) that there is no lawful ground of objection to the grant of a patent to us.

3. further declare that the inventor (s) for the said invention are:

   a) Dr. Noel John de Souza, Dr. Prasad Keshav Deshpande

   b) Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051, Maharashtra State, India.

   c) All Indian Nationals

4. We, claim the priority from the application(s) filed in convention countries, particulars of which are as follows :

   Not applicable

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/we are the applicant/patentee:

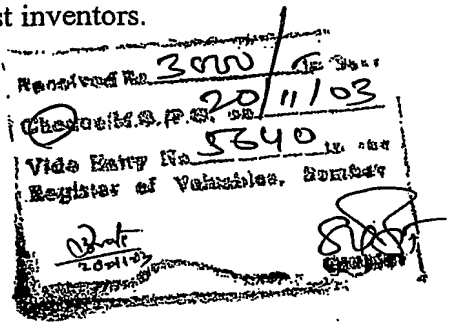
   Not applicable.

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on ____ under section 16 of the Act.

   Not applicable.

7. That we are the assignee or legal representative of the true and first inventors.

1199/mum/2003
20/11/2003



8. That our address for service in India is as follows:

Wockhardt Limited
Wockhardt Towers, Bandra-Kurla Complex
Bandra (E), MUMBAI 400 051
Tel. No. 022-6534444
Fax 022-6534242

9. Following declaration was given by the inventor(s):

We the true and first inventors for this invention declare that the applicant Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East), Mumbai 400 051 herein is our assignee.

Dr. Noel John de Souza _____

Dr. Prasad Keshav Deshpande _____

Dated this 20th day of November 2003

10. That to the best of our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application.

11. Following are the attachment with the application:

a) Provisional Specification – 2 copies
b) Form 2
c) Form 3

We request that a patent may be granted to us for the said invention.

Dated this 20th day of November 2003

Dr N J de Souza
Director-R&D

To: The Controller of Patents,
The Patents Office Branch, Mumbai.

FORM 2

THE PATENTS ACT, 1970
(39 of 1970)

PROVISIONAL SPECIFICATION
(See section 10)

1. **Title: 'A PROCESS FOR NOVEL POLYMORPHS OF (-)-1-CYCLOPROPYL-6-FLUORO-8-METHOXY-7-(4-AMINO-3,3-DIMETHYLPIPERIDIN-1-YL)-1,4-DIHYDRO-4-OXO-QUINOLINE-3-CARBOXYLIC ACID HYDROCHLORIDE AND MESYLATE SALTS'**

2. Wockhardt Limited, Wockhardt Towers, Bandra Kurla Complex, Bandra (East) Mumbai – 400 051, Maharashtra State, India, an Indian Company registered under the Companies Act 1956

The following specification describes the nature of the invention and the manner in which it is to be performed.

A PROCESS FOR NOVEL POLYMORPHS OF (-)-1-CYCLOPROPYL-6-FLUORO-8-METHOXY-7-(4-AMINO-3,3-DIMETHYLPIPERIDIN-1-YL)-1,4-DIHYDRO-4-OXO-QUINOLINE-3-CARBOXYLIC ACID HYDROCHLORIDE AND MESYLATE SALTS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application corresponds to U S patent application Serial No. 10/128,996 filed April 23, 2002 (PCT application Serial No. PCT/IN02/00111 filed April 23, 2002) and U S patent application Serial No. 10/318,367 filed December 12, 2002 (PCT application Serial No. PCT/IN03/00232 filed December 12, 2002). U S patent application Serial No. 10/128,996 claims priority from US provisional applications Serial Nos. 60/286,291 filed April 25, 2001, 60/287,104 filed April 27, 2001 and 60/341,165 filed December 13, 2001. U S patent application Serial No. 10/318,367 claims priority from US provisional application Serial No. 60/341,165 filed December 13, 2001. The contents of each of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

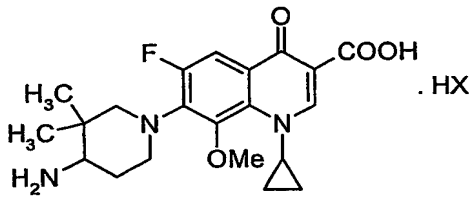
The present invention relates to novel polymorphs designated A-3 and A-4 for the hydrochloride salts of the levorotatory isomer (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid and to novel polymorphs designated B-1 and B-2 for the mesylate salts of the levorotatory isomer (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid. It also relates to processes for their preparation, to corresponding pharmaceutical compositions incorporating them and to their use as antimicrobials.

Polymorphs A-3 and A-4 of the respective hydrochloride salts of the levorotatory isomer (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid and polymorphs B-1 and B-2 of the respective

mesylate salts of the levorotatory isomer (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid are hereinafter all briefly named as "the compound/s of the invention".

BACKGROUND OF THE INVENTION

The fluoroquinolones, 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid hydrochloride and 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid methane sulfonate ("methane sulfonate" being also termed as "mesylate"), having the formula I and II below



Formula I HX = HCl
Formula II HX = CH_3SO_3H

are described in our pending U.S. Patent Application Nos. 10/128,996 and 10/318,367 and WO Application Nos. 02/085886 and 03/050107. Racemic and optically active enantiomeric forms of 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid are described in the said US patent applications and WO applications. Furthermore, in US application No. 10/318,367 and corresponding WO application 03/050107, the respective polymorphs A-1 and A-2 of the hydrochloride salt forms of the racemic mixture and enantiomeric isomers of 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid hydrochloride are also described.

The processes for preparing the respective hydrochloride and methane sulfonate salts of the racemic mixture and optical enantiomers of 1-cyclopropyl-6-fluoro-8-methoxy-7-

(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid are described in our pending US patent application No. 10/128,996 (the '996 application).

According to our pending US patent application No. 10/318,367 (the '367 application), the levorotatory enantiomer (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid hydrochloride is produced by the method of the '996 application. On dissolution in methanol and cooling, provided a polymorph designated A-1having a crystalline form, and characterized by X-ray powder diffraction spectroscopy, infrared spectroscopy and differential scanning calorimetry. The '367 application also describes a second polymorph designated A-2 having a crystalline form prepared by dissolving the levorotatory –1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid hydrochloride in 50% aqueous isopropanol and subsequent cooling, said A-2 crystalline polymorph being characterized by X-ray Powder Diffraction spectroscopy, infrared spectroscopy and differential scanning calorimetry.

Although our co-pending US patent application Nos. '996 and '367 describe mesylate salts of the racemic mixture and optical enantiomers of 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid, the applications do not describe that the said mesylate salts can exists in more than one polymorphic form.

The antibacterial activity of the compounds of the invention including the hereinbefore mentioned polymorphs A-1 and A-2 is described in our co-pending US patent application Nos. 10/128,996 and 10,318,367.

We have now found novel pharmaceutically suitable hydrochloride salt polymorphic forms (designated A-3 and A-4) and methane sulfonate salt polymorphic forms (designated B-1 and B-2) of the compound (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid and novel processes to prepare and isolate them. These polymorphic forms have the same

antibacterial activity of the compounds disclosed in our co-pending US patent application Nos. 10/128,996 and 10/318,367.

SUMMARY OF THE INVENTION

The present invention relates to (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride polymorph A-3 characterised by an X-ray powder diffraction pattern comprising peaks at (2θ): 7.04± 0.2°, 7.70± 0.2°, 8.06± 0.2°, 12.34± 0.2°, 12.78± 0.2°, 13.64± 0.2°, 15.40± 0.2°, 16.14± 0.2°, 18.62± 0.2°, 19.40± 0.2°, 20.64± 0.2°, 21.84± 0.2°, 23.22± 0.2°, 26.80± 0.2°, 27.88± 0.2°, 29.86± 0.2°, 32.30± 0.2°, 33.36± 0.2°, 37.02± 0.2°, 39.24± 0.2°;

DSC: endotherm at 131.66 °C (onset at 95.32 °C), exotherm at 202.16°C (onset at 198.36°C), endotherm at 257.33°C (onset at 252.35°C));

Infra–red spectrum selected peaks (cm^{-1}): 3396, 1715, 1621, 1530, 1451, 1274.

The present invention further relates to a process for making (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride polymorph A-3 comprising the steps of suspending or dissolving polymorphic form A-1 or A-2 of 1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid hydrochloride in water, if necessary by heating, to form a suspension or a solution; adding an organic solvent to the solution and isolating the polymorphic form A-3. In an alternate process polymorph A-1 can be dissolved in an aqueous solution of a salt of an inorganic acid, or a salt of an organic acid, or a sugar like dextrose, the solution allowed to cool and the crystals of the polymorphic form A-3 isolated.

The present invention also relates to (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride polymorph A-4 characterised by an X-ray powder diffraction pattern comprising peaks at (2θ): 5.34 ± 0.2°, 5.68 ± 0.2°, 9.48 ± 0.2°, 10.08 ± 0.2°, 10.44 ± 0.2°, 11.42 ± 0.2°, 11.84 ± 0.2°, 12.86 ± 0.2°, 13.62 ± 0.2°, 14.24 ± 0.2°, 14.74 ± 0.2°, 16.08 ± 0.2°, 22.16

± 0.2°, 24.14 ± 0.2°, 24.82 ± 0.2°, 25.94 ± 0.2°, 27.02 ± 0.2°, 28.84 ± 0.2°, 31.82 ± 0.2°;
DSC: endotherm at 254.33°C (onset at 248.00 °C);
Infra–red spectrum (cm^{-1}): 2895, 1729, 1618, 1516, 1452, 1379, 1321, 1179, 1108, 1050, 951, 882, 808, 734.

The present invention further relates to a process for making (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride polymorph A-4 comprising the steps of vacuum drying polymorphic forms A-1 or A-2 or A-3 at an elevated temperature for a time sufficient to effect transformation to polymorphic form A-4.

The present invention furthermore relates to (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate polymorph B-1 characterised by an X-ray powder diffraction pattern comprising peaks at (2θ): 8.02± 0.2°, 12.84± 0.2°, 14.70± 0.2°, 16.44± 0.2°, 17.30± 0.2°, 19.56± 0.2°, 20.90± 0.2°, 21.46± 0.2°, 23.76± 0.2°, 25.56± 0.2°, 27.30± 0.2°, 30.66± 0.2°, 37.46± 0.2°;
DSC: endotherm at 301.00 °C (onset at 297.58 °C);
Infra–red spectrum (cm^{-1}): 3441, 2956, 1735, 1617, 1517, 1447, 1321, 1231, 1141, 1043, 886, 821, 776.

The present invention furthermore relates to a process for making (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate polymorph B-1 comprising the steps of suspending or dissolving (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid in an organic solvent to form a suspension/solution, heating the suspension/solution to a temperature between about room temperature and efflux temperature of the solvent; adding methane sulfonic acid to the suspension/solution, heating the suspension/solution for a period of time sufficient to effect transformation to the mesylate polymorphic form B-1; and isolating the mesylate form B-1.

The present invention furthermore relates to (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate polymorph B-2 characterised by an X-ray powder diffraction pattern comprising peaks at (2θ): 9.38± 0.2°, 10.04± 0.2°, 12.28± 0.2°, 12.94± 0.2°, 13.98± 0.2°, 15.78± 0.2°, 16.86± 0.2°, 18.80± 0.2°, 19.62± 0.2°, 21.24± 0.2°, 22.32± 0.2°, 23.18± 0.2°, 24.64± 0.2°, 25.56± 0.2°, 28.44± 0.2°, 30.02± 0.2°, 30.90± 0.2°, 39.74± 0.2°;

DSC: exotherm at 83.83°C (onset at 58.11°C), endotherm at 305.50 °C (onset at 301.48 °C);

Infra–red spectrum (cm^{-1}): 3486, 1728, 1624, 1521, 1460, 1325, 1191, 1047, 879, 781.

The present invention furthermore relates to a process for making (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate polymorph B-2 comprising the steps of dissolving crystalline form B-1 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid mesylate in water, by heating if necessary, to form a solution; cooling the solution, adding an aqueous-miscible organic solvent, allowing to stand for a sufficient time to effect transformation to polymorphic form B-2; and isolating the mesylate polymorphic form B-2.

Furthermore, the present invention also provides pharmaceutical compositions comprising an antibacterially effective amount of polymorphs of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride and mesylate of formula I and II respectively as described above together with a pharmaceutically acceptable carrier, and a method for treating bacterial infection in a mammal which comprises administrating to a subject in need of such treatment a therapeutically or prophylactially effective amount of such a pharmaceutical composition.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will now be described in further detail with reference to the accompanying drawings.

FIG. 1 represents a characteristic X-ray powder diffraction (XRPD) spectrum of the crystalline A-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride prepared by the methods of our pending US application No. 10/318,367.

FIG. 2 represents a characteristic X-ray powder diffraction (XRPD) spectrum of the crystalline A-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride prepared by the methods of our pending US application No. 10/318,367.

FIG. 3 represents a characteristic X-ray powder diffraction (XRPD) spectrum of the crystalline A-3 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride prepared by the methods of the present invention.

FIG. 4 represents a characteristic Differential Scanning Calorimetric (DSC) thermogram of the crystalline A-3 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride of the invention.

FIG. 5 represents a characteristic Infra-red (IR) spectrum of the crystalline A-3 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride of the invention.

FIG. 6 represents a characteristic X-ray powder diffraction (XRPD) spectrum of the crystalline A-4 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride of the invention.

FIG. 7 represents the Differential Scanning Calorimetric (DSC) thermogram of the crystalline A-4 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride of the invention.

FIG. 8 represents the Infra-red (IR) spectrum of the crystalline A-4 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride of the invention.

FIG. 9 represents the X-ray powder diffraction (XRPD) spectrum of the crystalline B-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate of the invention.

FIG. 10 represents the Differential Scanning Calorimetric (DSC) thermogram of the crystalline B-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate of the invention.

FIG. 11 represents the Infra-red (IR) spectrum of the crystalline B-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate of the invention.

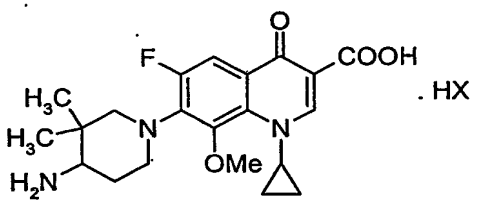
FIG. 12 represents the X-ray powder diffraction (XRPD) spectrum of the crystalline B-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid mesylate of the invention.

FIG. 13 represents the Differential Scanning Calorimetric (DSC) thermogram of the crystalline B-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate of the invention.

FIG. 14 represents the Infra-red (IR) spectrum of the crystalline B-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid methane sulfonate of the invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel polymorphs of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride selected from the group consisting of polymorph A-3 and polymorph A-4 thereof having formula I, and to polymorphs of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate selected from the group consisting of polymorph B-1 and polymorph B-2 thereof, having formula II:

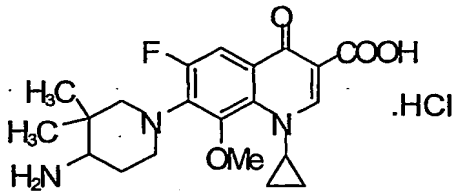


Formula I HX = HCl
Formula II HX = CH_3SO_3H

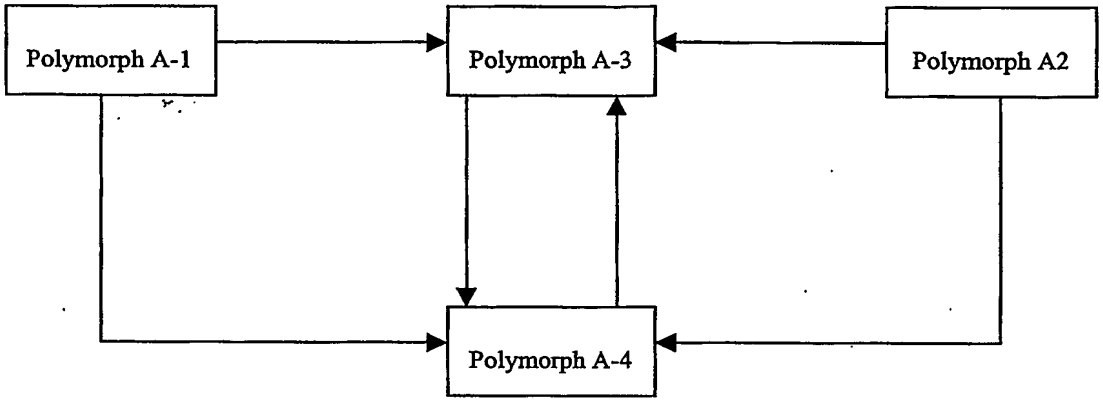
and pharmaceutical compositions comprising polymorphs A-3, A-4, B-1, B-2 and methods for using them.

The present invention further relates to processes for preparing polymorphs A-3, A-4, B-1 and B-2 as illustrated in the following reaction Scheme-I

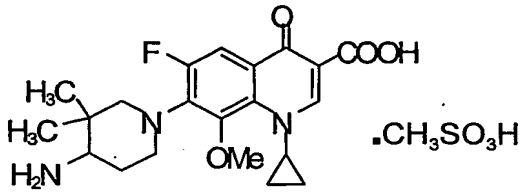
Scheme-I



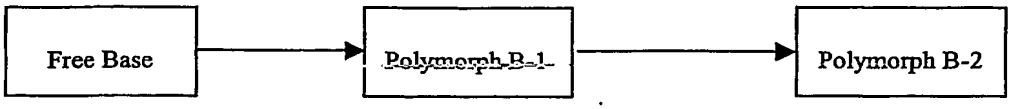
Formula I



Scheme-II



Formula II



Referring to Scheme-I, polymorph A-3 is prepared in one sequence from polymorph A-1. Polymorph A-1 may be prepared according to the method of Example 105 of our pending US patent application No. 10/318,367, the disclosure of which is hereby incorporated herein by reference in its entirety. Polymorphic form A-1 of (-)-1-

cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride, having X-ray powder diffraction spectrum as shown in Fig. 1, is suspended or dissolved in water, if necessary by heating at 25 – 100 °C, maintaining with stirring at that temperature for a period of time between 0.5 to 12 hours to form a suspension or a solution and adding a water-miscible organic solvent. Suitable solvents include C_1-C_6 alkanols, preferably isopropanol, or acetonitrile, or C_3-C_6 aliphatic ketones, preferably acetone. The resulting mixture is stirred for a sufficient period of time, preferably upto 12 hours to effect the transformation completely to polymorphic form A-3, and recovering the polymorphic form A-3 as a crystal upon cooling the solution. The resultant crystals are dried to a constant weight to yield the polymorph A-3 of the invention.

X-ray powder diffraction (2θ): 7.04± 0.2°, 7.70± 0.2°, 8.06± 0.2°, 12.34± 0.2°, 12.78± 0.2°, 13.64± 0.2°, 15.40± 0.2°, 16.14± 0.2°, 18.62± 0.2°, 19.40± 0.2°, 20.64± 0.2°, 21.84± 0.2°, 23.22± 0.2°, 26.80± 0.2°, 27.88± 0.2°, 29.86± 0.2°, 32.30± 0.2°, 33.36± 0.2°, 37.02± 0.2°, 39.24± 0.2°;

DSC: endotherm at 131.66 °C (onset at 95.32 °C) exotherm at 202.16°C (onset at 198.36°C), endotherm at 257.33°C (onset at 252.35°C));

Infra–red spectrum selected peaks (cm^{-1}): 3396, 1715, 1621, 1530, 1451, 1274.

Alternatively, polymorph A-1 may also be converted to polymorph A-3 by dissolving A-1 in an aqueous solution of a salt of an inorganic acid, preferably sodium chloride, optionally by heating if necessary, to obtain a clear solution, maintaining the solution at temperatures of 3 – 5 °C to effect the transformation completely to polymorphic form A-3, and recovering the polymorphic form A-3 as a crystal. The resultant crystals are dried to a constant weight to yield the polymorph A-3 of the invention.

According to Scheme-I, polymorphic form A-3 may also be formed is a second sequence from Polymorphic form A-2. Polymorph A-2 may be prepared according to the method of Example 106 of our pending US patent application No. 10/318,367, the disclosure of which is hereby incorporated herein by reference in its entirety. Polymorphic form A-2 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-

dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride, having X-ray powder diffraction spectrum as shown in Fig. 2, is suspended or dissolved in water, if necessary by heating at 80 – 100 °C to form a solution, cooling to a temperature of 30 – 40 °C and adding a water-miscible organic solvent. Suitable solvents include C_1-C_6 alkanols, preferably isopropanol. The resulting mixture is stirred for a sufficient period of time, preferably upto 12 hours to effect the transformation completely to polymorphic form A-3, and recovering the polymorphic form A-3 as a crystal upon cooling the solution. The resultant crystals are dried to a constant weight to yield the polymorph A-3 of the invention.

Referring to Scheme I, polymorph A-4 is prepared from polymorphs A-1, A-2 and A-3 by vacuum drying polymorphic forms A-1 or A-2 or A-3 at an elevated temperature, preferably 130°C upto 150°C optionally under reduced pressure for a time, preferably upto 12 hours, sufficient to effect transformation to polymorphic form A-4, and recovering the polymorphic form A-4 as a crystalline solid.

X-ray powder diffraction (2θ): 5.34 ± 0.2°, 5.68 ± 0.2°, 9.48 ± 0.2°, 10.08 ± 0.2°, 10.44 ± 0.2°, 11.42 ± 0.2°, 11.84 ± 0.2°, 12.86 ± 0.2°, 13.62 ± 0.2°, 14.24 ± 0.2°, 14.74 ± 0.2°, 16.08 ± 0.2°, 22.16 ± 0.2°, 24.14 ± 0.2°, 24.82 ± 0.2°, 25.94 ± 0.2°, 27.02 ± 0.2°, 28.84 ± 0.2°, 31.82 ± 0.2°;

DSC: endotherm at 254.33°C (onset at 248.00 °C);

Infra–red spectrum (cm^{-1}): 2895, 1729, 1618, 1516, 1452, 1379, 1321, 1179, 1108, 1050, 951, 882, 808, 734.

Polymorph A-4 can be converted to polymorph A-3 according to a third sequence in Scheme-I, by treatment with water and isopropanol as indicated above with respect to the conversion of polymorph A-2 to polymorph A-3. The water may be in the form of liquid or vapour.

Referring to Scheme-II, polymorph B-1 is prepared from (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid. (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-

1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid, described as Example 17 in our pending US application Nos. 10/128,996 and 10/318,367, is suspended or dissolved in a suitable organic solvent such as C_1-C_6 alkanols, preferably isopropanol or C_1-C_6 alkyl esters of C_1-C_6 alkanoic acids, preferably ethyl acetate, or acetonitrile to form a suspension/solution, heating the suspension/solution to a temperature between about 25 °C and 80 °C; adding methane sulfonic acid to the suspension/solution, heating at a temperature of 70 – 80 °C for a period of time, preferably 1 hour, sufficient to effect transformation to the mesylate polymorphic form B-1; and recovering the polymorphic form B-1 as a crystal upon cooling the solution. The resultant crystals are dried to a constant weight to yield the polymorph B-1 of the invention.

X-ray powder diffraction (2θ): 8.02± 0.2°, 12.84± 0.2°, 14.70± 0.2°, 16.44± 0.2°, 17.30± 0.2°, 19.56± 0.2°, 20.90± 0.2°, 21.46± 0.2°, 23.76± 0.2°, 25.56± 0.2°, 27.30± 0.2°, 30.66± 0.2°, 37.46± 0.2°;

DSC: endotherm at 301.00 °C (onset at 297.58 °C).

Infra–red spectrum (cm^{-1}): 3441, 2956, 1735, 1617, 1517, 1447, 1321, 1231, 1141, 1043, 886, 821, 776.

Referring to Scheme II, polymorph B-2 is prepared from polymorph B-1 by dissolving crystalline polymorphic form B-1 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline–3-carboxylic acid mesylate in water by heating at a temperature between 25 – 100 °C, preferably 80 – 100 °C to form a solution; cooling the solution to 25 – 35 °C and adding an aqueous-miscible organic solvent. A suitable organic solvent includes C_1-C_6 alkanols, preferably isopropanol, or C_3-C_6 aliphatic ketones, preferably acetone, or acetonitrile. The reaction mixture is allowed to stand for a sufficient time to effect transformation to polymorphic form B-2, and subsequent recovery of the polymorphic form B-2 as a crystal upon cooling. The resultant crystals are dried to a constant weight to yield the polymorph B-2 of the invention.

X-ray powder diffraction (2θ): 9.38± 0.2°, 10.04± 0.2°, 12.28± 0.2°, 12.94± 0.2°, 13.98± 0.2°, 15.78± 0.2°, 16.86± 0.2°, 18.80± 0.2°, 19.62± 0.2°, 21.24± 0.2°, 22.32± 0.2°, 23.18± 0.2°, 24.64± 0.2°, 25.56± 0.2°, 28.44± 0.2°, 30.02± 0.2°, 30.90± 0.2°, 39.74±

0.2°;

DSC: exotherm at 83.83°C (onset at 58.11°C), endotherm at 305.50 °C (onset at 301.48 °C);

Infra–red spectrum (cm^{-1}): 3486, 1728, 1624, 1521, 1460, 1325, 1191, 1047, 879, 781.

The antibacterial polymorphic compounds of the invention of formula I and II that can be synthesized using the methods and intermediates of this invention are useful in the treatment of mammals having a broad spectrum of bacterial infections as extensively described in the co-pending US patent applications 10/128,996 and 10/318,367.

The present invention also encompasses an antiinfective composition for the treatment of humans and animals in need of prophylaxix and/or therapy for systemic or topical infections especially resistant gram-positive organism infections, gram-negative organism infections, mycobacterial infections and nosocomial pathogen infections, which composition comprises an amount of a compound of the invention, the derivatives, isomers, salts, polymorphs, pseudopolymorphs, and hydrates thereof, substantially sufficient to eradicate said infection, but not to cause any undue side effects. Compounds and compositions of this invention can be administered to humans and animals who are at risk of being infected, for example a compound or composition of this invention can be administered to a patient prior to and/or after surgery.

In addition the compounds of the invention have superior bactericidal activity against pneumococci and streptococci of various groups. Cidal features available in such molecules add to their clinical attractiveness as it would offer clinicians a valuable treatment option to treat a broader range of infections caused by staphylococci, MRSA, MRSE, pneumococci, streptococci, mycobacteria and diverse range of anaerobic bacteria of clinical importance in a situation such as patients allergic to ß-lactam or possibility of infections due to macrolide resistant strains of streptococci and pneumococci or MRSA/QRSA. For anaerobic bacterial infections, currently available treatment options are rather limited due to reasons such as inadequate potency or gaps in the spectrum of anaerobic pathogens covered. Such is the case with macrolides.

With β-lactam antibacterials, the major shortcoming is their liability to a variety of β-lactamases, the drug inactivating enzymes elaborated by commonly encountered anaerobic pathogens. Older fluoroquinolones such as ciprofloxacin, levofloxacin, pefloxacin also suffered due to inadequate anti-anaerobic potency. The molecules of invention demonstrate several distinct gains in antimicrobial properties against anaerobic pathogens vis-à-vis earlier antibacterial agents of the β-lactam, macrolide and fluoroquinolone classes.

It has been found that the compounds of this invention, and compositions containing these compounds, are effective antimicrobial agents against a broad range of pathogenic microorganisms with advantages in low susceptibility to microbial resistance, reduced toxicity, and improved pharmacology.

Moreover, the molecules of the invention, chiral compounds, salts, polymorphs, pseudopolymorphs and hydrates thereof, also retain the other valuable features, of being bactericidal to fluoroquinolone resistant staphylococci (QRSA with resistant gyrase) and even to staphylococcal and pneumococcal isolates possessing Nor A efflux pumps and other efflux pumps. The compounds of the invention also display efflux pump inhibitory activity. A combination of all these properties coupled with overall good safety and tolerability observed in a new molecule renders them worthy of therapeutic use in humans and animals. By virtue of such features, they have considerable advantages over existing fluoroquinolone antibacterials, in particular in the treatment of respiratory diseases and infections of skin and soft tissue.

The above list of pathogens is merely by way of example and is in no way to be interpreted as limiting. Streptococci are implicated as one of the most common pathogens, in both the pediatric and adult population in diverse infections/diseases. Examples which may be mentioned of diseases, which can thus be prevented, alleviated and/or cured by the formulations according to the invention include but are not limited to are meningitis, otitis externa, otitis media; pharyngitis; pneumonia; life-threatening bacteremia, peritonitis; pyelonephritis; cystitis; endocarditis; systemic

infections; bronchitis; arthritis; local infections; and septic diseases. Several molecules of the present inventions also exhibit impressive gains in potency against *Mycobacterium tuberculosis* and therefore of potential value in the treatment of latent and recalcitrant mycobacterial infections such as tuberculosis.

These findings have an important implication from the point of view of the systemic use of the compounds of the invention in view of their superior potency, superior bactericidal activity, expanded biospectrum, better bioavailability and improved tolerability which are now enabled to be administered systemically in therapeutically effective doses.

Utilizing the compounds of the invention or the substantially optically pure or optically pure isomers, the derivatives and salts thereof, whether in systemic or topical dosage form, results in clearer dose-related definitions of efficacy, diminished toxic effects and accordingly an improved therapeutic index.

The present invention encompasses certain compounds, dosage forms, and methods of administering the compounds to a human or other animal subject. Specific compounds and compositions to be used in the invention must, accordingly, be pharmaceutically acceptable. As used herein, such a "pharmaceutically acceptable" component is one that is suitable for use with humans and / or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

The pharmaceutical compositions are prepared according to conventional procedures used by persons skilled in the art to make stable and effective compositions. In the solid, liquid, parenteral and topical dosage forms, an effective amount of the active compound or the active ingredient is any amount, which produces the desired results.

For the purpose of this invention the pharmaceutical compositions may contain the active compounds of the invention, their derivatives, salts and hydrates thereof, in a

form to be administered alone, but generally in a form to be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. Suitable carriers which can be used are, for example, diluents or excipients such as fillers, extenders, binders, emollients, wetting agents, disintegrants, surface active agents and lubricants which are usually employed to prepare such drugs depending on the type of dosage form. Any suitable route of administration may be employed for providing the patient with an effective dosage of the compound of the invention their derivatives, salts and hydrates thereof. For example, oral, rectal, parenteral (subcutaneous, intramuscular, intravenous), transdermal, topical and like forms of administration may be employed. Dosage forms include (solutions, suspensions, etc) tablets, pills, powders, troches, dispersions, suspensions, emulsions, solutions, capsules, injectable preparations, patches, ointments, creams, lotions, shampoos and the like.

The prophylactic or therapeutic dose of the compounds of the invention, their derivatives, salts or hydrates thereof, in the acute or chronic management of disease will vary with the severity of condition to be treated, and the route of administration. In addition, the dose, and perhaps the dose frequency, will also vary according to the age, body weight and response of the individual patient. In general, the total daily dose range, for the compounds of the invention, the derivatives, salts or hydrates thereof, for the conditions described herein, is from about 200 mg to about 1500 mg, in single or divided doses. Preferably, a daily dose range should be between about 400 mg to 1200 mg, in single or divided dosage, while most preferably a daily dose range should be between about 500 mg to about 1000 mg in divided dosage. While intramuscular administration may be a single dose or up to 3 divided doses, intravenous administration can include a continuous drip. It may be necessary to use dosages outside these ranges in some cases as will be apparent to those skilled in the art. Further, it is noted that the clinician or treating physician will know how and when to interrupt, adjust, or terminate therapy in conjunction with individual patient's response. The term "an amount sufficient to eradicate such infections but insufficient to cause undue side effects" is encompassed by the above – described dosage amount and

dose frequency schedule.

Pharmaceutical compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, or tablets, or aerosol sprays, each containing a predetermined amount of the active ingredient, as a powder or granules, or as a solution or a suspension in an aqueous liquid, a non-aqueous liquid, an oil-in-water emulsion, or a water-in-oil liquid emulsion. Such compositions may be prepared by any of the methods of pharmacy, but all methods include the step of bringing into association the active ingredient with the carrier, which constitutes one or more necessary ingredients. In general, the compositions are prepared by uniformly and intimately admixing the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product into the desired presentation.

The compositions of the present invention include compositions such as suspensions, solutions, elixirs, aerosols, and solid dosage forms. Carriers as described in general above are commonly used in the case of oral solid preparations (such as powders, capsules and tablets), with the oral solid preparations being preferred over the oral liquid preparations. The most preferred oral solid preparation is tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are employed. Examples of suitable carriers include excipients such as lactose, white sugar, sodium chloride, glucose solution, urea, starch, calcium carbonate, kaolin, crystalline cellulose and silicic acid, binders such as water, ethanol, propanol, simple syrup, glucose, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methyl cellulose, potassium phosphate and polyvinyl pyrrolidone, disintegrants such as dried starch, sodium alginate, agar powder, laminaria powder, sodium hydrogen carbonate, calcium carbonate, Tween (fatty acid ester of polyoxyethylenesorbitan), sodium lauryl sulfate, stearic acid monoglyceride, starch, and lactose, disintegration inhibitors such as white sugar, stearic acid glyceryl ester, cacao butter and hydrogenated oils, absorption promoters such as quaternary ammonium bases and

sodium lauryl sulfate, humectants such as glycerol and starch, absorbents such as starch, lactose, kaolin, bentonite and colloidal silicic acid, and lubricants such as purified talc, stearic acid salts, boric acid powder, polyethylene glycol and solid polyethylene glycol.

The tablet, if desired, can be coated, and made into sugar-coated tablets, gelatin-coated tablets, enteric-coated tablets, film-coated tablets, or tablets comprising two or more layers.

If desired, tablets may be coated by standard aqueous or non-aqueous techniques.

In molding the pharmaceutical composition into pills, a wide variety of conventional carriers known in the art can be used. Examples of suitable carriers are excipients such as glucose, lactose, starch, cacao butter, hardened vegetable oils, kaolin and talc, binders such as gum arabic powder, tragacanth powder, gelatin, and ethanol, and disintegrants such as laminaria and agar.

In molding the pharmaceutical composition into a suppository form, a wide variety of carriers known in the art can be used. Examples of suitable carriers include polyethylene glycol, cacao butter, higher alcohols, gelatin, and semi-synthetic glycerides.

A second preferred method is parenterally for intramuscular, intravenous or subcutaneous administration.

A third preferred route of administration is topically, for which creams, ointments, shampoos, lotions, dusting powders and the like are well suited. Generally, an effective amount of the compound according to this invention in a topical form is from about 0.1% w/w to about 10 % w/w of the total composition. Preferably, the effective amount of the compound of the invention is 1% w/w of the total composition.

In addition to the common dosage forms set out above, the compounds of the present invention may also be administered by controlled release means and/or delivery devices such as those described in U.S. Patent Nos. 3,845,770; 3,916,899; 3,536,809; 3,598,123 and 4,008,719; the disclosures of which are hereby incorporated by reference.

Desirably, each tablet contains from about 200 mg to about 1500 mg of the active ingredient. Most preferably, the tablet, cachet or capsule contains either one of three dosages, about 200 mg, about 400 mg, or about 600 mg of the active ingredient.

When the pharmaceutical composition is formulated into an injectable preparation, in formulating the pharmaceutical composition into the form of a solution or suspension, all diluents customarily used in the art can be used. Examples of suitable diluents are water, ethyl alcohol, polypropylene glycol, ethoxylated isostearyl alcohol, polyoxyethylene sorbitol, and sorbitan esters. Sodium chloride, glucose or glycerol may be incorporated into a therapeutic agent.

The antimicrobial pharmaceutical composition may further contain ordinary dissolving aids, buffers, pain-alleviating agents, and preservatives, and optionally coloring agents, perfumes, flavors, sweeteners, and other drugs.

For topical application, there are employed as non-sprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, e.g. preservatives, antioxidants, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient preferably in combination with a solid or liquid inert carrier material.

A specific embodiment of the invention is the preparation of storage stable compositions of the compounds of the invention of formula I. Such stable compositions can be advantageously made through the use of selective stabilizers. Different stabilizers are known to those skilled in the art of making pharmaceutical compositions. Of special utility for making storage stable compositions of the compound of the invention of formula I, stabilizers such as disodium ethylenediaminetetraacetic acid (EDTA), tromethamine, cyclodextrins such as gamma-cyclodextrin, hydroxy-propyl-gamma-cyclodextrin have been found to be useful.

In a specific embodiment of the invention, the pharmaceutical compositions contain an effective amount of the active compounds of the invention, its derivatives, salts or hydrates thereof described in this specification as hereinbefore described in admixture with a pharmaceutically acceptable carrier, diluent or excipients, and optionally other therapeutic ingredients.

The invention is further defined by reference to the following examples describing in detail the preparation of the composition of the present invention as well as their utility. It will be apparent to those skilled in the art that many modifications, both to materials and methods may be practiced without departing from the purpose and scope of this invention.

The following preparations and examples illustrate the methods of preparation of the compounds of the invention and are provided only as examples, but not to limit the scope of the compounds of the invention.

TEST EXAMPLE-1

X-ray Powder Diffraction Analysis of the forms of the invention

Approximately 300 mg of the test sample was thinly spread on a sample holder. X-ray powder diffraction analyses (40kv x 40 mA Rigaku D/max 2200) were performed under

the conditions listed below:

Scan speed 5°/ min

Sampling time 7 min

Scan mode: continuous

2θ/θ reflection

Cu target (Ni filter)

TEST EXAMPLE-2

Thermal Analysis of the forms the invention:

For the Differential Scanning Calorimetry, PERKIN-ELMER DSC 7 system was used. 3-5 mg of the teat sample was weighed into the aluminum pan, press sealed with an aluminium lid. After three tiny needle holes were made on the lid, the sample was analyzed by heating from 30°C to 300°C at a rate of 10°C/min.

TEST EXAMPLE-3

Infra-red spectrum analysis of the forms the invention:

Infra –red spectrum was obtained on BRUKER VECTOR 22 system and by using KBr pellet.

PREPARATIONS

The polymorphs A-1 and A-2 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline -3-carboxylic acid hydrochloride were prepared as per Example Nos. 105 and 106 respectively described in our co-pending US Patent application No. 10/318,367. The X-ray powder diffraction spectra of polymorphs A-1 and A-2 are shown in Figures 1 and 2 respectively.

The free base (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline -3-carboxylic acid was prepared as per Example No.17 described in our co-pending US Patent applications Nos. 10/128,996 and 10/318,367.

EXAMPLE 1

Polymorphic form A-3 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-1

Method-A

A suspension of A-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (150 gm) in water (450 ml) was stirred at 25-35 °C for 3 hours. Isopropanol (2.5 ltr) was added to the suspension. The reaction mixture was stirred further for 12 hours and the crystals of the titled product isolated by filtration and dried under vacuum at a temperature between 60 to 70 °C. Yield 120 gms, 80%.

The product is characterized by the X-ray diffraction pattern described above.

Analysis:

X-ray powder diffraction (2θ): 7.04± 0.2°, 7.70± 0.2°, 8.06± 0.2°, 12.34± 0.2°, 12.78± 0.2°, 13.64± 0.2°, 15.40± 0.2°, 16.14± 0.2°, 18.62± 0.2°, 19.40± 0.2°, 20.64± 0.2°, 21.84± 0.2°, 23.22± 0.2°, 26.80± 0.2°, 27.88± 0.2°, 29.86± 0.2°, 32.30± 0.2°, 33.36± 0.2°, 37.02± 0.2°, 39.24± 0.2°;

DSC: endotherm at 131.66 °C (onset at 95.32 °C) exotherm at 202.16°C (onset at 198.36°C), endotherm at 257.33°C (onset at 252.35°C));

Infra–red spectrum selected peaks (cm^{-1}): 3396, 1715, 1621, 1530, 1451, 1274.

Method-B

Polymorph A-1 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (100 mg) was dissolved in 0.9 % aqueous solution of sodium chloride (10 ml) to obtain a

clear solution, which was allowed to stand at 3 – 5°C. Crystals of the titled product which separated from the solution were isolated by filtration and dried under vacuum at a temperature between 60 to 70 °C. Yield 76 mg, 76%.

The product is characterized as polymorph A-3 according to the analytical data as shown for the product obtained under Method-A.

EXAMPLE 2

Polymorphic form A-3 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-2

A suspension of polymorph A-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (1 gm) in water (3 ml) was heated under stirring at a temperature between 90-100 °C to provide a clear solution. The clear solution was allowed to cool and isopropanol (20 ml) was added. The resulting suspension was stirred at a temperature between 25-35 °C for 1 hour and the crystals of the titled product isolated by filtration and dried under vacuum at a temperature between 60 to 70 °C. Yield 0.78 gm, 78% having analytical data as described in Example 1.

EXAMPLE-3

Polymorphic form A-3 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-4

A suspension of polymorphic A-4 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (1.5 gm) in water (5 ml) was heated under stirring at a temperature between 90-100 °C to provide a clear solution. The clear solution was allowed to cool to 25 – 35 °C and isopropanol (50 ml) was added. The resulting suspension was stirred for 1 hour and the crystals of the titled product isolated by filtration and dried under

vacuum at a temperature between 60 to 70 °C. Yield 1.21 gm, 81% having analytical data as described in Example 1.

EXAMPLE-4

Polymorphic form A-4 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-1

The polymorphic A-1 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (7.5gm) was kept at a temperature between 130 to 135 °C for 3- 4 hours to provide a form A-4 in quantitative yield.

The product is characterized by the X-ray diffraction pattern described above.

Analysis:

X-ray powder diffraction (2θ): 5.34 ± 0.2°, 5.68 ± 0.2°, 9.48 ± 0.2°, 10.08 ± 0.2°, 10.44 ± 0.2°, 11.42 ± 0.2°, 11.84 ± 0.2°, 12.86 ± 0.2°, 13.62 ± 0.2°, 14.24 ± 0.2°, 14.74 ± 0.2°, 16.08 ± 0.2°, 22.16 ± 0.2°, 24.14 ± 0.2°, 24.82 ± 0.2°, 25.94 ± 0.2°, 27.02 ± 0.2°, 28.84 ± 0.2°, 31.82 ± 0.2°;

DSC: endotherm at 254.33°C (onset at 248.00 °C);

Infra–red spectrum (cm^{-1}): 2895, 1729, 1618, 1516, 1452, 1379, 1321, 1179, 1108, 1050, 951, 882, 808, 734.

EXAMPLE-5

Polymorphic form A-4 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-2

The polymorphic A-2 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (5 gm) was kept at a temperature between 130 to 135 °C for 3- 4 hours to provide a form A-4 in quantitative yield having analytical data described in Example 4.

EXAMPLE-6

Polymorphic form A-4 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid hydrochloride from Polymorphic form A-3

The polymorphic A-3 form of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid hydrochloride (5 gm) was kept at a temperature between 130 to 135 °C for 3- 4 hours to provide a form A-4 in quantitative yield having analytical data described in Example 4.

EXAMPLE-7

Polymorphic form B-1 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate

A suspension of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid (12 gms, 29.77 mmol) in isopropanol (150 ml) was heated to reflux at 75-80 °C under stirring. Methane sulfonic acid (3.2 gms, 32.74 mmol) was added to the suspension. The reaction mixture was stirred at a temperature between 75-80 °C for 1 hour. The suspension was cooled to a temperature between 25-35 °C and the crystals of the titled product isolated by filtration and dried under vacuum at a temperature between 60 to 70 °C. Yield 14 gms, 94%.
The product is characterized by the X-ray diffraction pattern described above.
Analysis:
X-ray powder diffraction (2θ): 8.02± 0.2°, 12.84± 0.2°, 14.70± 0.2°, 16.44± 0.2°, 17.30± 0.2°, 19.56± 0.2°, 20.90± 0.2°, 21.46± 0.2°, 23.76± 0.2°, 25.56± 0.2°, 27.30± 0.2°, 30.66± 0.2°, 37.46± 0.2°;
DSC: endotherm at 301.00 °C (onset at 297.58 °C).
Infra–red spectrum (cm^{-1}): 3441, 2956, 1735, 1617, 1517, 1447, 1321, 1231, 1141, 1043, 886, 821, 776.

EXAMPLE - 8

Polymorphic form B-2 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline –3-carboxylic acid mesylate from Polymorphic form B-1:

Crystalline form B-1 of (-)-1-cyclopropyl-6-fluoro-8-methoxy-7-(4-amino-3,3-dimethylpiperidin-1-yl)-1,4-dihydro-4-oxo-quinoline-3-carboxylic acid mesylate (2.0 gms, 4.04 mmol) was stirred in 3 ml water at a temperature between 80- 100 °C under stirring to give a clear solution. The clear solution was cooled to 25- 35 °C to provide a thick suspension. The thick suspension was stirred for 1 hour after adding 30 ml isopropanol at a temperature between 25-35 °C and the crystals of the titled product isolated by filtration and dried under vacuum at a temperature between 60 to 70 °C. Yield 1.7 gms, 85%.

The product is characterized by the X-ray diffraction pattern described above.

Analysis:

X-ray powder diffraction (2θ): 9.38± 0.2°, 10.04± 0.2°, 12.28± 0.2°, 12.94± 0.2°, 13.98± 0.2°, 15.78± 0.2°, 16.86± 0.2°, 18.80± 0.2°, 19.62± 0.2°, 21.24± 0.2°, 22.32± 0.2°, 23.18± 0.2°, 24.64± 0.2°, 25.56± 0.2°, 28.44± 0.2°, 30.02± 0.2°, 30.90± 0.2°, 39.74± 0.2°;

DSC: exotherm at 83.83°C (onset at 58.11°C), endotherm at 305.50 °C (onset at 301.48 °C);

Infra–red spectrum (cm^{-1}): 3486, 1728, 1624, 1521, 1460, 1325, 1191, 1047, 879, 781.

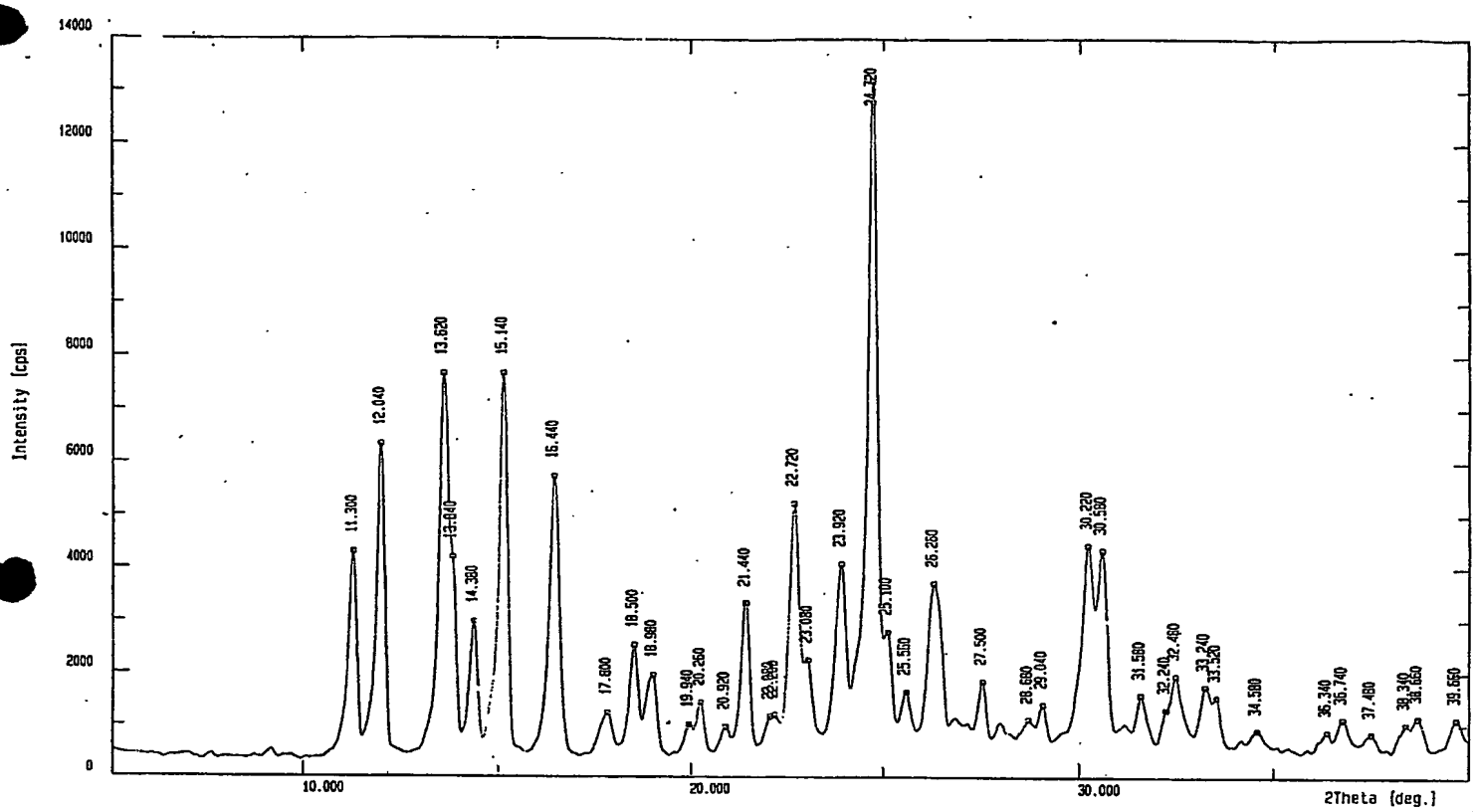


FIG. 1 X - ray powder diffraction (XRPD) spectrum of the hydrochloride salt, polymorph A-1

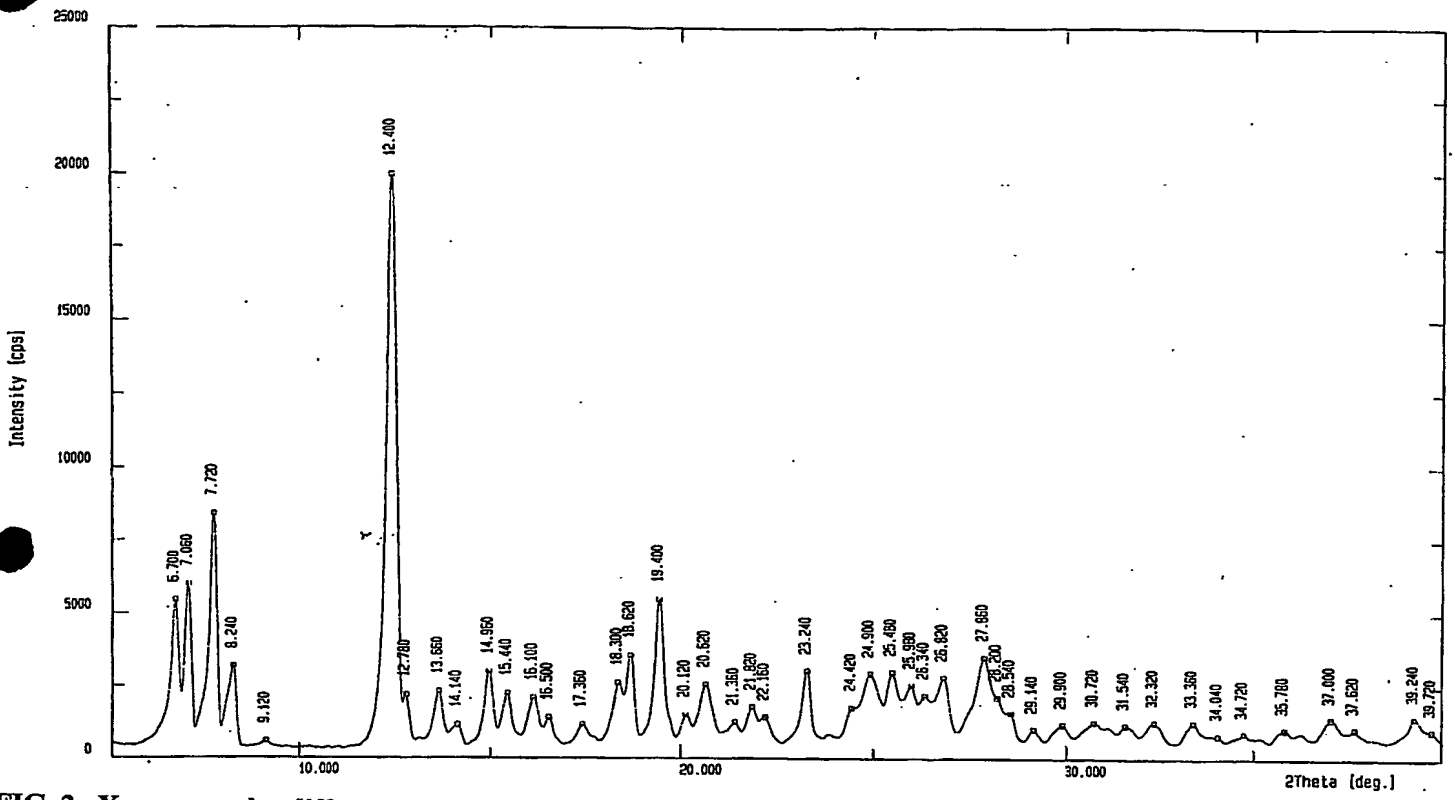
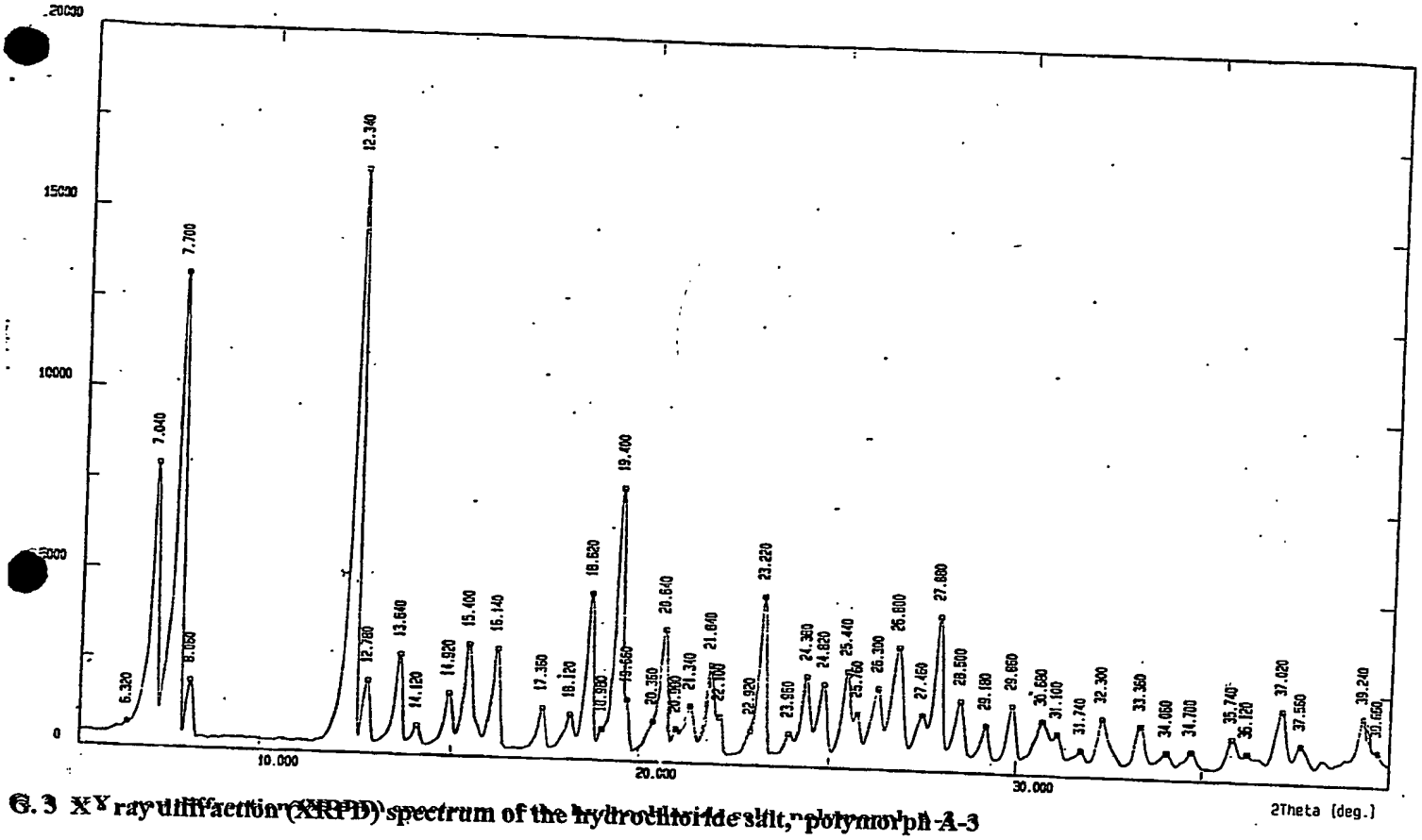


FIG. 2 X - ray powder diffraction (XRPD) spectrum of the hydrochloride salt, polymorph A-2



G. 3 X-ray diffraction (XRPD) spectrum of the hydrochloride salt, polymorph A-3

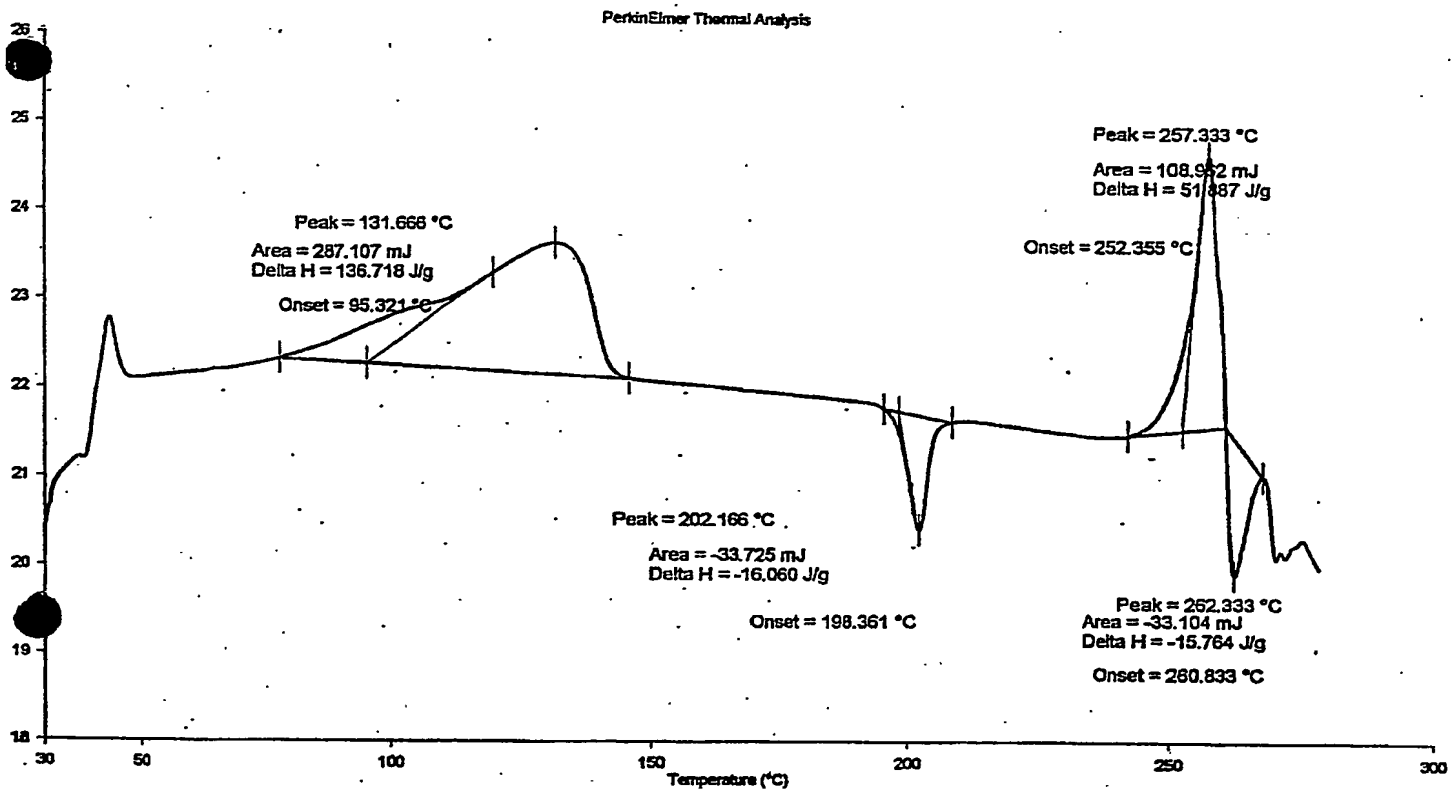
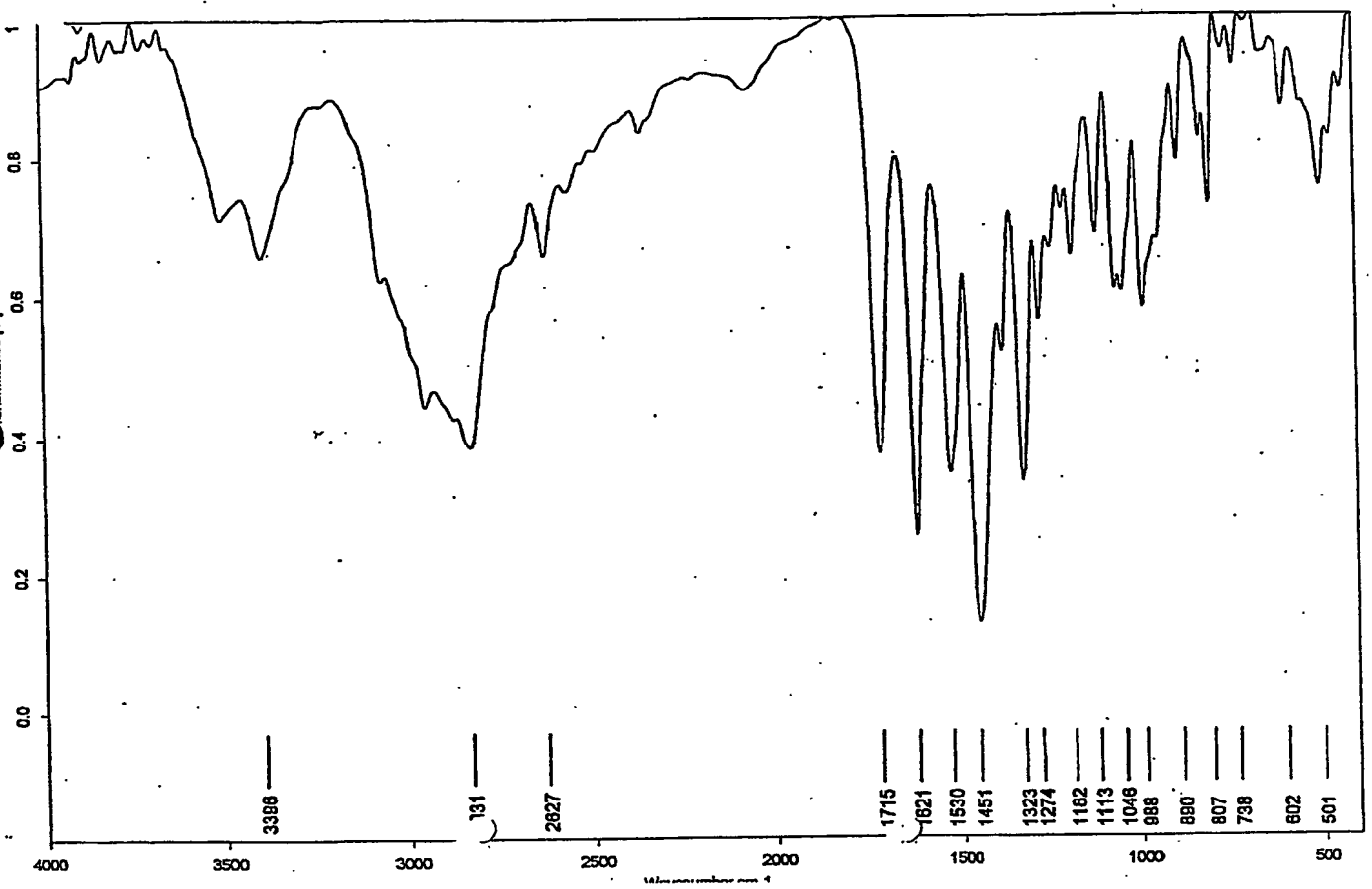


FIG. 4 Differential scanning calorimetric (DSC) thermogram of the hydrochloride salt, polymorph A-3

FIG. 5 Infra - red (IR) spectrum of the hydrochloride salt, polymorph A-3



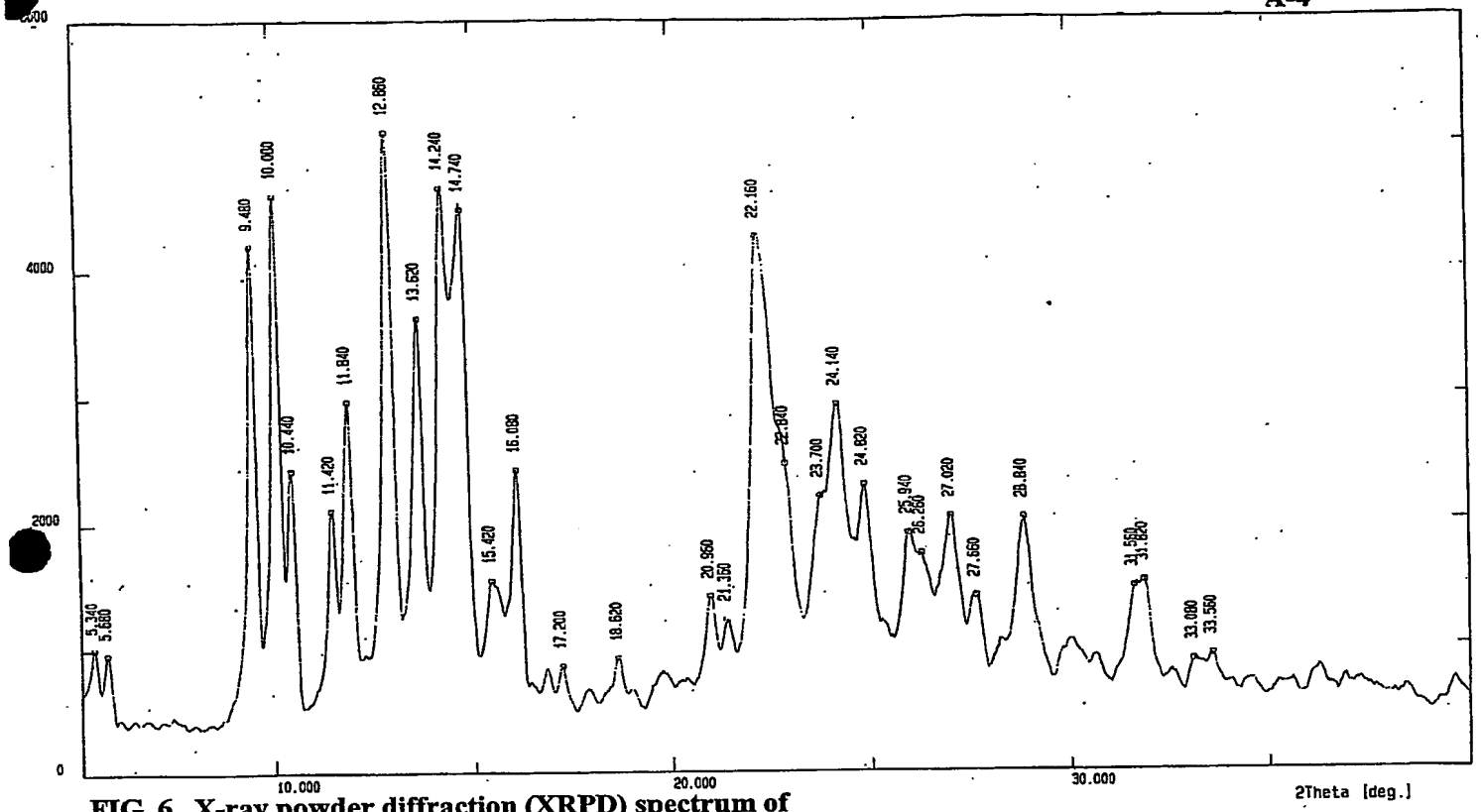


FIG. 6 X-ray powder diffraction (XRPD) spectrum of the hydrochloride salt, polymorph A-4

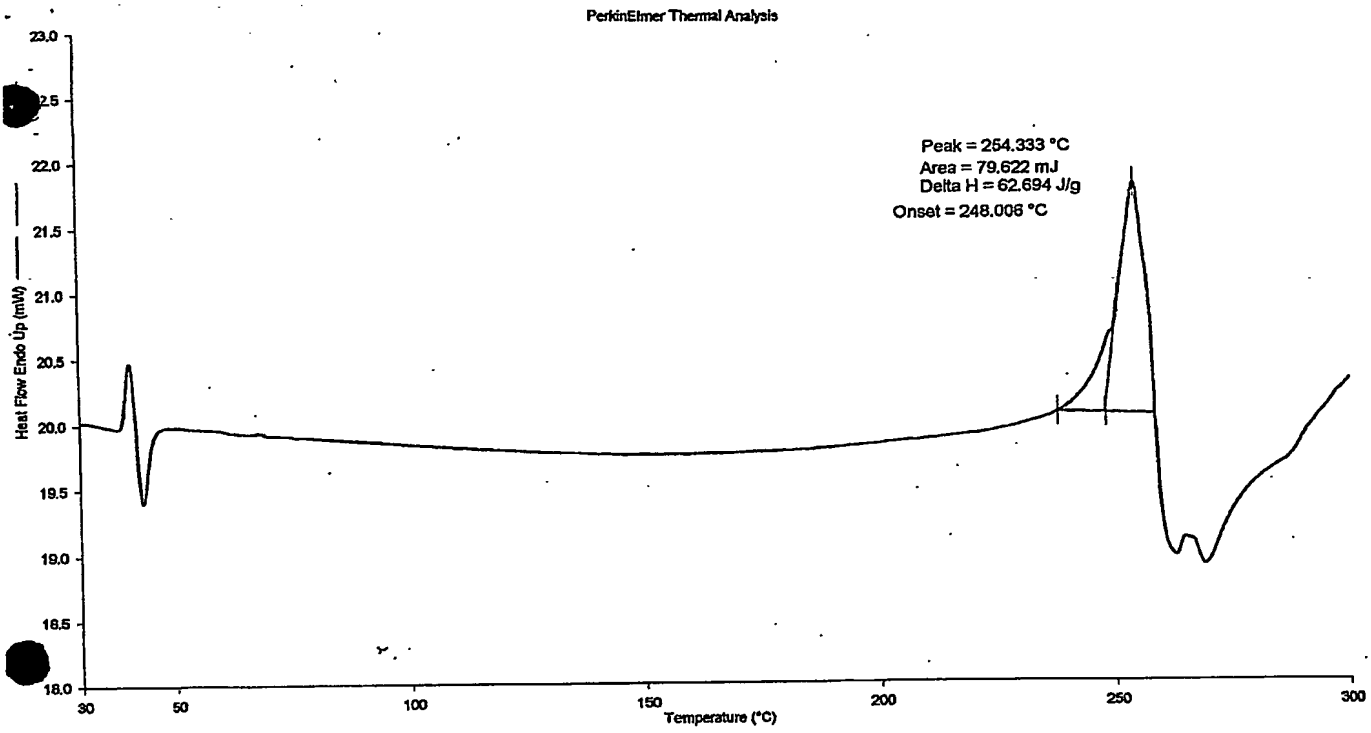


FIG. 7 Differential scanning calorimetric (DSC) thermogram of the hydrochloride salt, polymorph A-4

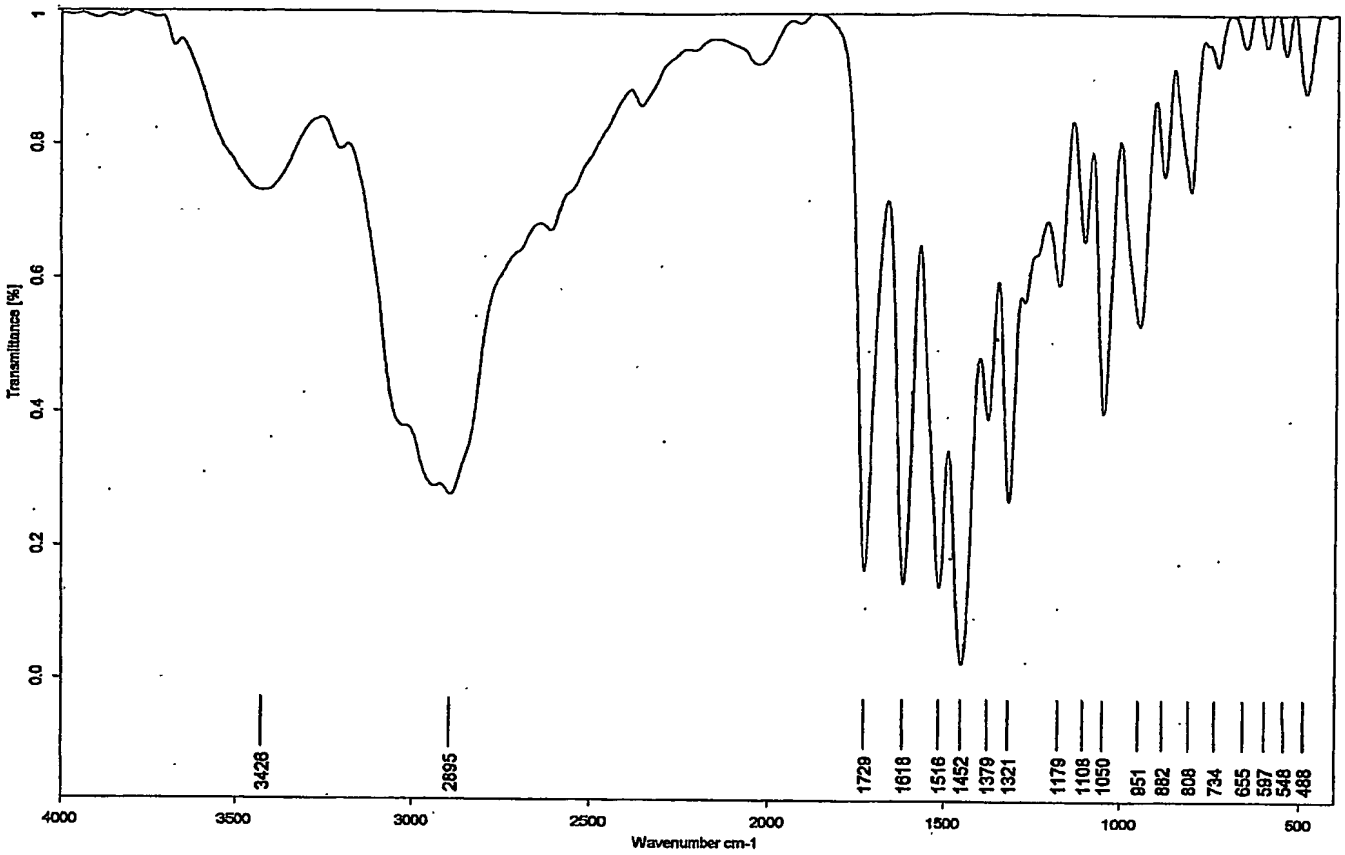


FIG. 8 Infra - red (IR) spectrum of the hydrochloride salt, polymorph A-4

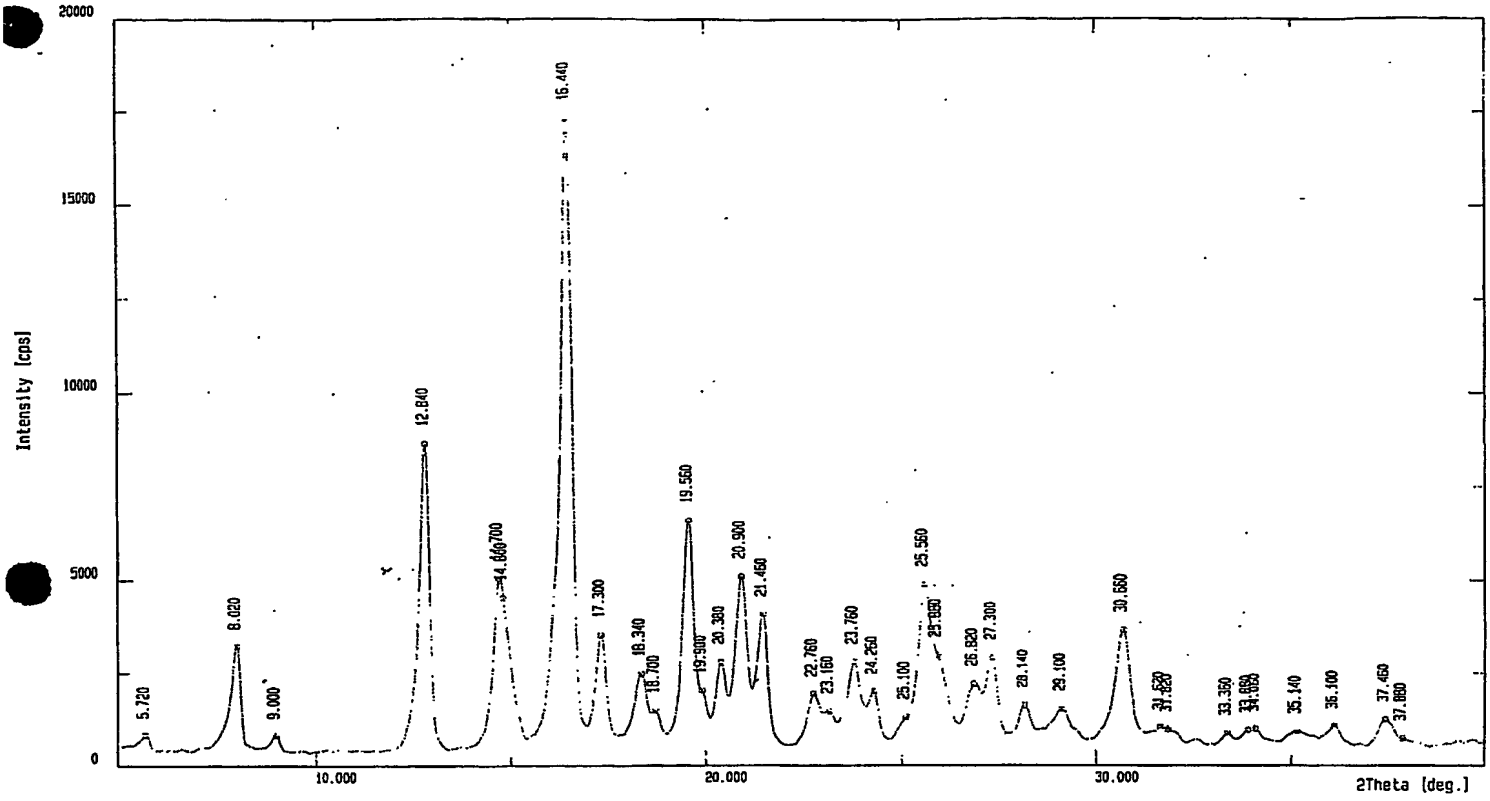


FIG. 9 X = ray powder diffraction (XRPD) spectrum of the mesylate salt, polymorph B-1

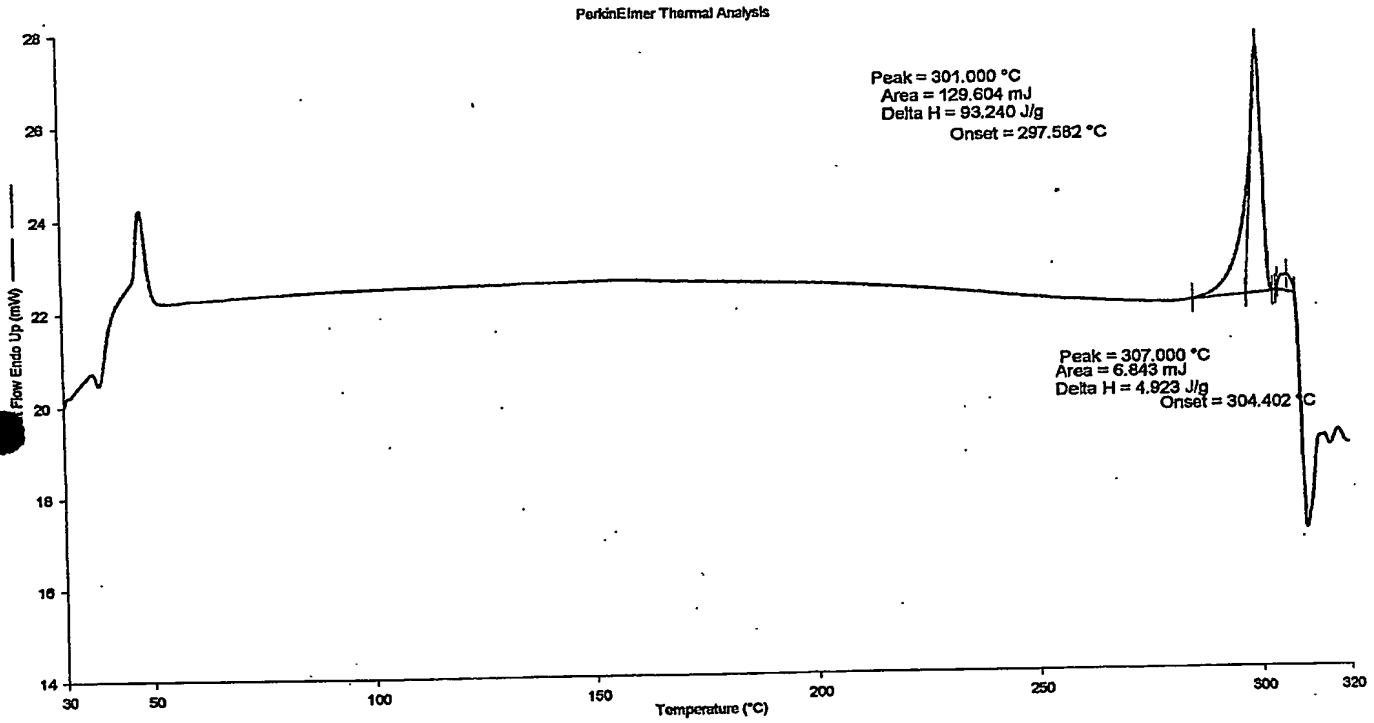


FIG. 10 Differential scanning calorimetric (DSC) thermogram of the mesylate salt, polymorph B-1

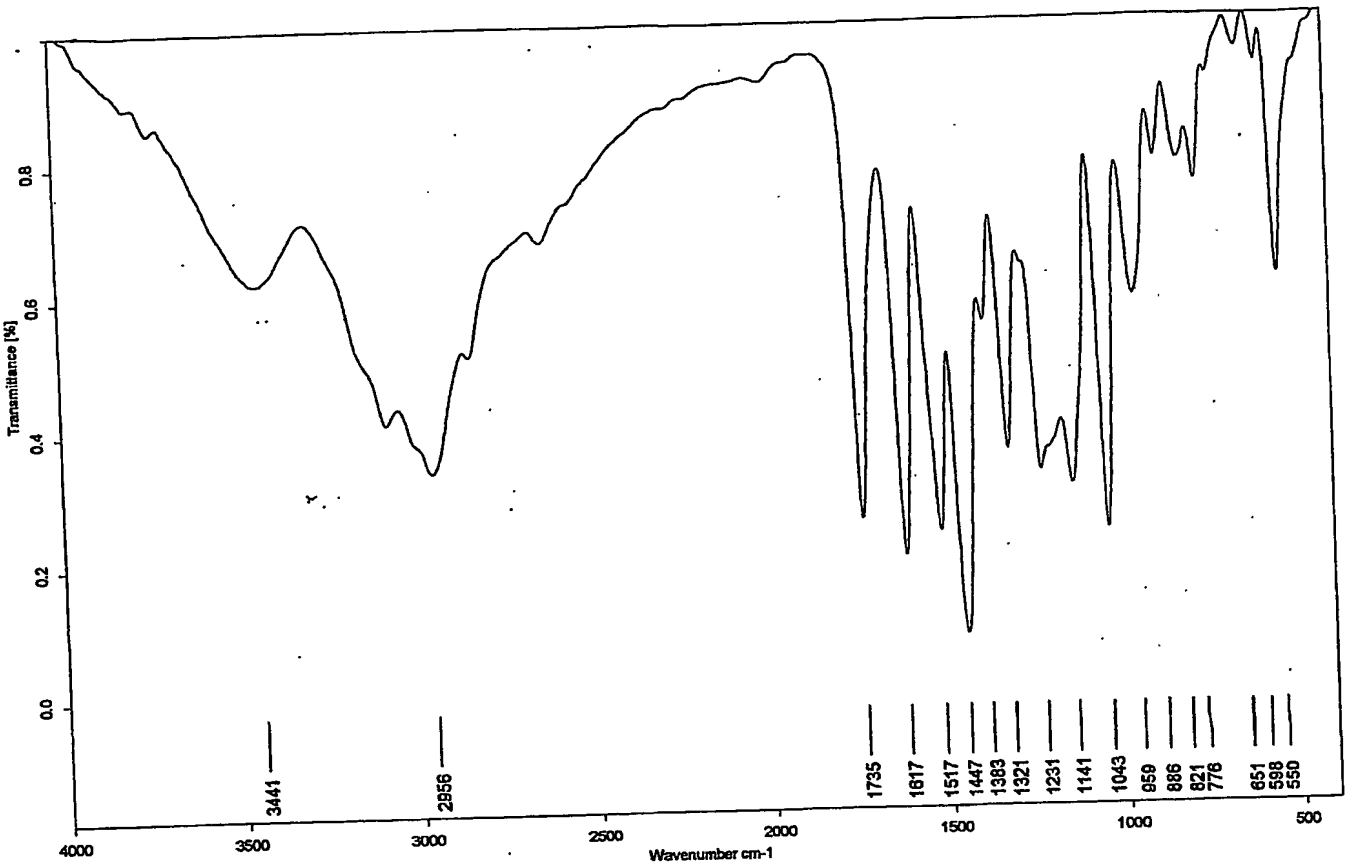


FIG. 11 Infra - red (IR) spectrum of the mesylate salt, polymorph B-1

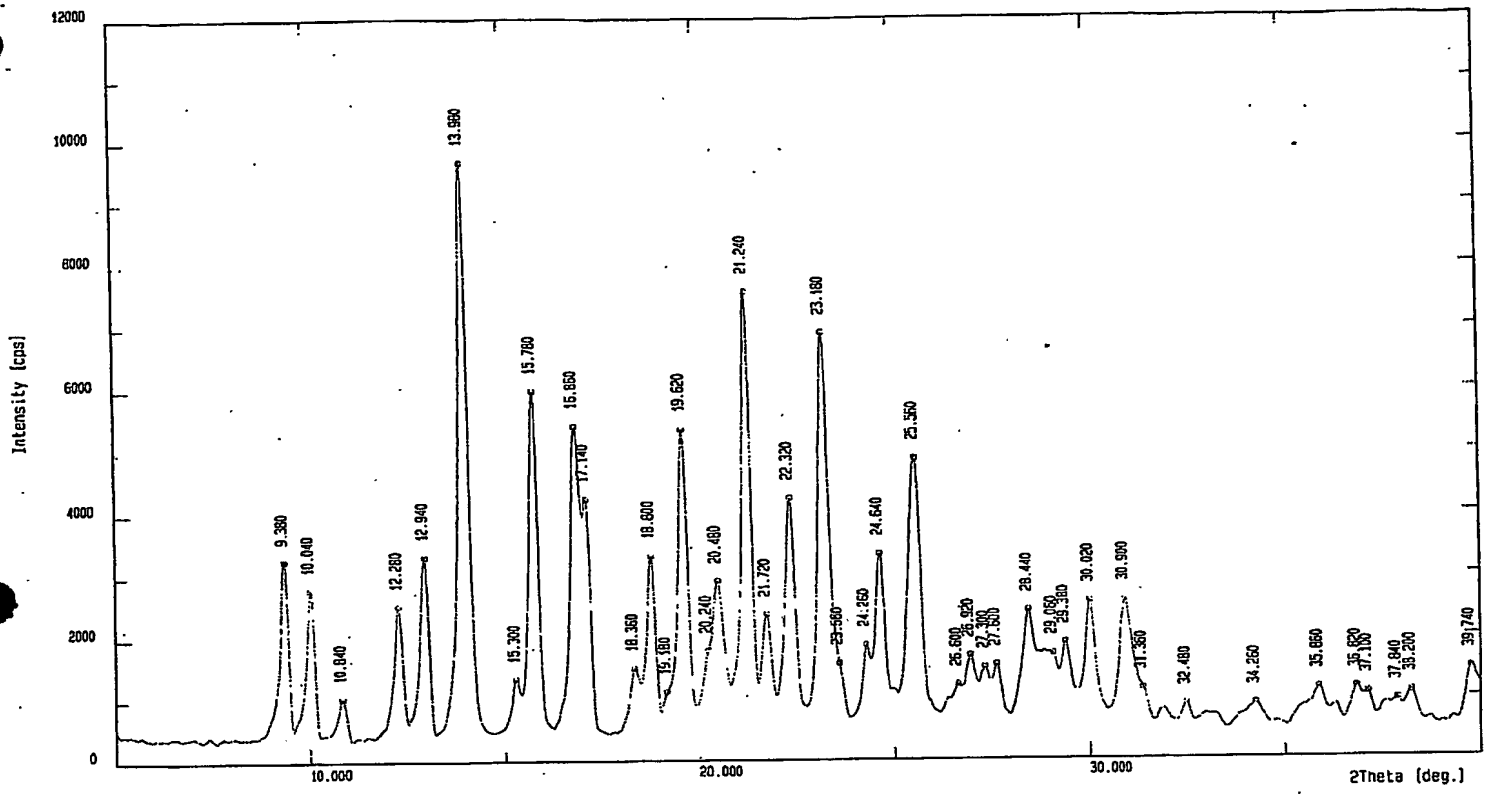


FIG. 12 X - ray powder diffraction (XRPD) spectrum of the mesylate salt, polymorph B-2

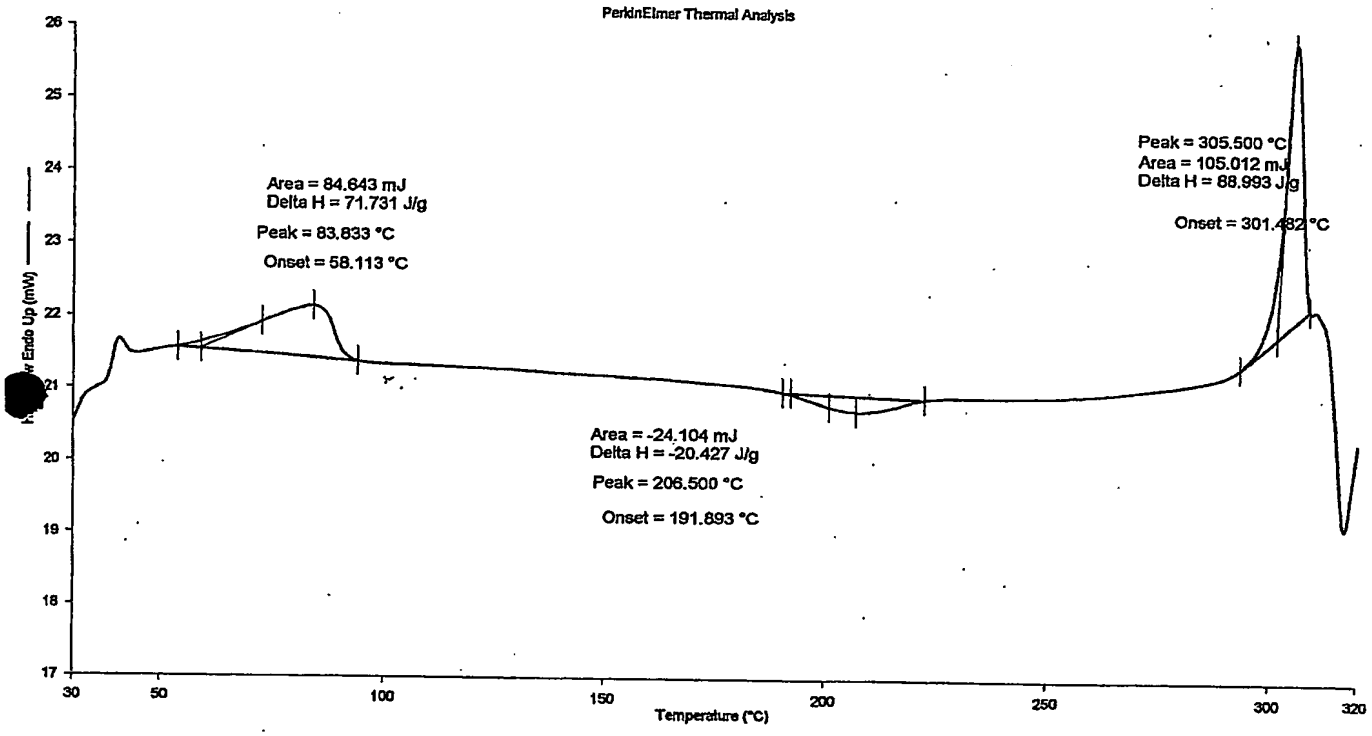


FIG. 13 Differential scanning calorimetric (DSC) thermogram of the mesylate salt, polymorph B-2

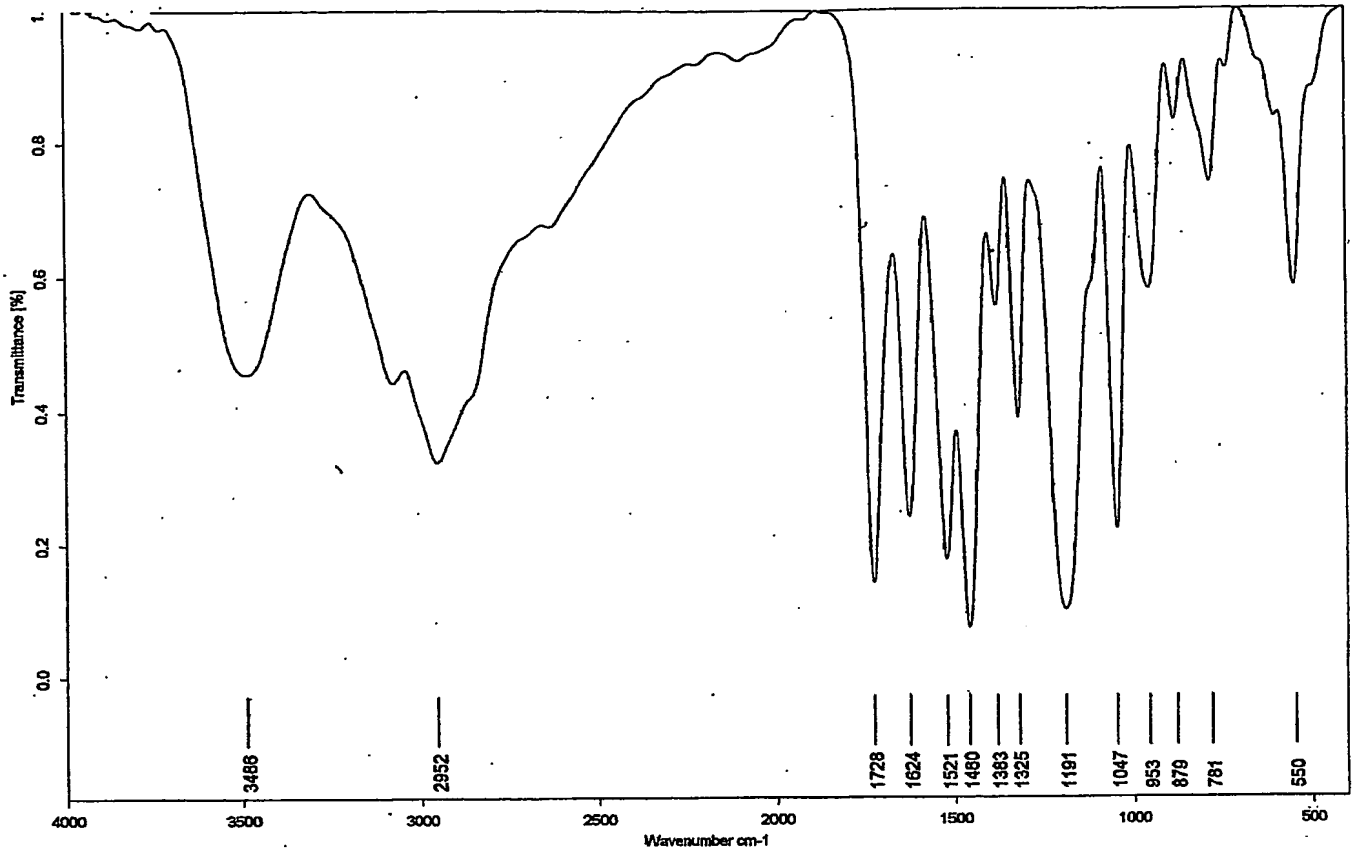


FIG. 14 Infra - red (IR) spectrum of the mesylate salt, polymorph B-2

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